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BIOLOGICAL STANDARDIZATION OF THE DIGITALIS BODIES BY THE CAT METHOD OF HATCHER.

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Since the publication of this method by Hatcher and Brody [1] a number of observers have subjected it to more or less unfavorable criticism and it is the purpose of the present communication to discuss these criticisms and to subject the method to an even more rigorous scrutiny, comparing it with some of the other and more widely used methods, in order to determine which of them is the most serviceable. Much of the material is drawn from reports found in the literature, or from the laboratory records of several who have carried out many series of standardizations on cats, and the rest from the personal experiences of the author.

Before passing to an analysis it seems advisable to outline the important factors which must be considered of value in any method. These desiderata are:

1. The method should be reasonably accurate and give fairly concordant results on repeated tests of the same preparation.

2. Results obtained with the same preparation tested at long intervals of time should be strictly comparable, and deteriorations, if present, should be detected.

3. It should, as far as possible, eliminate adventitious factors such as might cause variations in the results, e.g., absorption, climatic effects, seasonal changes, etc.

4. Range of applicability; it should be equally applicable to the

[1] A. J. PHARM.; 1910; 82; p. 360.

testing of most, or all, of the numerous digitalis bodies, pure principles, galenicals, proprietary preparations, and the specialties.

5. It should afford a means of comparing widely different members of the group, both as to their relative activity and their probable toxicity for man.

6. The results of the evaluations should be more or less fully transferable to man.

7. It should test that action of the drug upon which its therapeutic use depends.

8. It should be sufficiently simple to be mastered by the relatively inexperienced so that its use may be wide.

9. It should be humane.

10. It should not be too time consuming.

11. It should not be too costly.

It is in the light of these desiderata that the cat method will be criticised and compared with the other commonly used methods. Those with which it will be compared are: 1. the twelve hour frog method of Houghton [2]; 2. the one hour frog method of Famulener and Lyons [3]; 3. and the guineapig method of Reed and Vanderkleed.[4] No discussion of the technical details of the several methods will be given, for it is taken for granted that those to whom this comparison will be of interest are more or less familiar with these details, and the references cited will provide others with the facts as described by the several authors.

As the cat method is the one which is to be subjected to criticism and compared with the other methods, I will present a number of standardizations made by it and taken at random to provide material for analysis. These are given in Table 1.

TABLE 1.

MISCELLANEOUS ASSAYS.

Exp.	Drug	Dose in Mg. X kg.	Average	Maximum variation from average in per cent.
	Ouabain A			
1		0.086		
2		0.110		
3		0.090		
4		0.099		
5		*0.069		

[2] A. J. PHARM.; 1909; 81; p. 461.

[3] Proc. Am. Pharm. Ass.; 1902; L; 415.

[4] A. J. PHARM.; 1908; 80; p. 110.

Exp.	Drug	Dose in Mg. X kg.	Average	Maximum Variation from average in per cent.
	Ouabain A.—*Cont'd.*			
6		0.085	0.098	33.6%
7		0.110		
8		0.102		
9		* 0.067		
10		0.110		
11		* 0.131		
12		0.116		
	Ouabain B			
1		0.101		
2		0.122	0.109	11.9%
3		0.105		
4		0.109		
	Convallamarin			
1		1.51		
2		1.78	1.68	10.1%
3		1.77		
	Fluidextract Squill			
1		545		
2		645	580	11.2%
3		525		
4		595		
	Fluidextract Apocynum			
1		65.0		
2		67.5		
	Tinct. Digitalis Ger. A			
1		122		
2		137		
3		117	120.8	13.4%
4		119		
5		108		
6		122		
	Tinct. Digitalis B			
1		57.7		
2		54.8	57.7	5%
3		60.6		
	Tinct. Strophanthus			
1		2.44		
2		3.40		
	Fluidext. Adonis, very old			
1		880		
2		700	895	21.7%
3		1045		
4		755		
	Adonidin			
1		3.75		

Exp.	Drug	Dose in Mg. X kg.	Average	Maximum variation from average in per cent.
	Adonidin—*Cont'd.*			
2		4.28		
3		5.10	4.34	17.4%
4		3.58		
5		5.00		
	Helleborein			
1		1.66		
2		1.70	1.88	31.3%
3		2.47		
4		1.72		
	Digitalein			
1		3.7		
2		3.2		
3		3.5	3.47	7.7%
4		3.45		
5		3.5		

Criticisms and Comparisons.

The first of the desiderata is that the method shall be reasonably accurate and give fairly concordant results on repeated tests of the same preparation. Reference to the table will immediately give the idea that the cat method fails in the first and most important requirement. Careful consideration, however, will show this to be an impression rather than a fact. For example, in series A of ouabain the maximum variation from the average dose as determined by the twelve tests is 33.6 per cent. of the average. Further, each of the starred experiments varies from the average dose of the series by at least 30 per cent. These are very great variations for a test which is to establish a standard, but if the average of the entire twelve be taken as the result of the standardization of the specimen, which is in fact precisely what is done in any method of biological assay, it will be seen to lie only 2 per cent. below the average determined by a very large number of series of tests made over several years (see H. & B.[1]).

It will be shown that in this or any other biological method of assay a certain number of animals will be found to be either tolerant or susceptible to the action of a given drug. Thus, in each of several series of experiments reported by Hatcher and Brody [1] such variations were seen and from these I will cite the following example: Four cats received digitalinum verum requiring 1.50, 1.52, 1.56, and 1.80 mg. per kilogramme, respectively, to cause death,

last animal being abnormal in reaction. It is, therefore, obvious that one must not trust the reaction of a single animal, or take the average of the results of tests on two animals which show considerable variation. In view of this fact one should discard those results which were obtained upon animals showing obvious abnormality of response. Such a practice is common to all of the methods of assay here considered and is an entirely justifiable procedure.

Applying this means of rendering the use of animals more exact, from a quantitative point of view, to the series under discussion, one would have to discard the three starred experiments before making his calculations. The average dose calculated from the remaining nine tests is 0.100 mg. per kg. of cat, which is precisely the average previously determined for this specimen of ouabain. With this correct average and the three very abnormal results discarded there is still a maximum variation from the average of 16 per cent. in the case of one experiment. This may be explained on the ground of season, a matter to be discussed subsequently.

When the same arguments and methods of correction are applied to some of the other series we see how much greater is the accuracy of the cat method than was at first thought. Thus, in series B of ouabain experiment 2 was obviously made on an abnormal cat and when discarded from the calculation the variation between the three experiments remaining falls to 3.8 per cent. of the average. Again, in the series with helleborein, the figure 2.47 is obviously far too high and the animal from which it was obtained was certainly tolerant. With it eliminated the maximum variation from the corrected average is only 1.7 per cent. of the average.

I might here state that in a series of standardizations of 24 different specimens, including many different types of digitalis bodies and extending over nearly two years, variations were found ranging from less than one per cent. up to 17.4 per cent. of the average taken in each series. The average variation was 6.1 per cent. for the entire 24 series of tests.

In carrying out the cat method of standardization in actual practice at least three animals are used and if all three give closely similar results the average is taken as being correct. If two of the results are quite close but the third is considerably at variance a fourth, or even a fifth, test is made before an average is struck.

An exception to the use of three tests is sometimes made when the first two are found to give very closely similar results, as for

example, in the cases of apocynum and the tincture of strophanthus cited in the table. Even in such circumstances, if the test is one of a preparation for use in man, or of one which is wholly unknown as to approximate cat unit, a number of tests is always made for the sake of greater accuracy and certainty.

It may be contended that two of the three or four cats which are employed in a routine assay might readily be abnormal in reaction, and in the same direction. This would, to a certain extent, be an invalidating feature of the method if such an occurrence were likely, but it is, fortunately, an almost impossible accident, for it has not been possible to find an abnormal reaction of thirty per cent. or over in more than eight animals in 300; that is, only 2.7 per cent. of all cats are found to be very abnormal in reaction. This group of 300 experiments is made up by beginning at the latest series and counting back for nearly two years, including every experiment in each series of tests. The figure is therefore a fairly trustworthy index of the frequency of occurrence of decidedly abnormal animals. No evidence is to be found in this series to show that either tolerance or susceptibility is the predominant abnormality, hence the chance of two animals falling in a single series and having the same type of abnormality of reaction is very slight indeed. Just such a rare coincidence was observed, and is shown in series A of the ouabain tests given in the table, experiments 5 and 9. This was a long series and the three abnormal experiments present are seen to have been scattered throughout the group, so that had any set of four or five tests been made these abnormal reactions would have been recognized as such and due allowance made for them.

Comparing the variations encountered in the cat method with some of the reported results of the frog methods of testing, or with the guineapig method, we find that 6 out of 60 frogs showed an error of from 9 to 10.6 per cent.[5] Hale asserts[6] that the frog method gives, "an estimate of the amount of glucosides in a solution to within a few (1-10) per cent. of absolute accuracy." But Vanderkleed[7] has shown that with uniform conditions the lethal dose of ouabain for female frogs is about 19 per cent. greater than for males.

How these variations compare with the results obtained by the

[5] A. J. PHARM.; 1911; 83; p. 97.
[6] Hygien, Lab. Bull.; No. 74; 1911.
[7] A. J. PHARM.; 1912; 84; p. 14.

cat method will be seen by consulting the figures for the different standardizations of ouabain made at different times and often with "unknown solutions." For example, the two series reported in the table show the following: 1. If the uncorrected results are used the average of the first series falls only 2 per cent. below the established standard, while that of the second series lies 9 per cent. above this standard. 2. When the averages taken are based upon the corrected series (after the elimination of the very abnormal animals) A shows an absolutely correct result and B gives a figure 5 per cent. above the standard. Ouabain is selected to show the extent of the variations obtained by standardizations made at different times because it is the purest of the isolated glucosides and is the least liable to variation in its strength. Similar close estimations have been found in repeated tests of a great many other digitalis bodies made in this laboratory, the results often being obtained by several different observers and with "unknowns." An instance of this is found in the case of the digitalis leaf which supplied the tincture marked Ger. A. This leaf yielded an assay of approximately 120 mg. per kg. of cat as its unit when other preparations were used—both tinctures and infusions.

The guineapig method is stated [8] to provide a means of making preparations, "which are always within ten per cent. of the same strength." But Haskell [9] expresses his belief in the variability of guineapigs and says, "I have been unable to find the report of a single series of experiments performed with the object of showing that guineapigs are not fully as much influenced by adventitious circumstances as are frogs." Vanderkleed [7] replies to this assertion citing the results of a series of 43 tests in which only one animal showed a variation as great as 10.4 per cent. Houghton [10] found these animals unsatisfactory, and Hale [5] says, "certain animals survived doses 20 per cent. larger than had killed others. Thus, 4 were killed with 0.5 mg. per gram of body weight, 3 lived with 0.6 mg. doses of the same drug." Lastly, Haskell [11] reports several series of standardizations of ouabain on guineapigs and shows the occurrence of variations, under similar conditions, ranging from 11 to 30 per cent. of the average found in the series under con-

[8] A. J. PHARM.; 1910; 82; p. 453.
[9] A. J. PHARM.; 1911; 83; p. 201.
[10] *J.A.M.A.*, 1898, xxxi; 959.
[11] A. J. PHARM.; 1912; 84; p. 241.

sideration. He remarks that, "the individual variation of guinea-pigs is by no means inconsiderable."

With regard to the individual variations and the effects these may have upon the ultimate accuracy of the estimations by the several different methods of biological assay there would seem to be rather wide fluctuations. But by the judicious application of the pruning knife of reason the markedly abnormal animals can be discarded, be they frogs, guineapigs, or cats, and the final results will show that each method affords a means of determining the strength of a given preparation with a limit of error of not over ten per cent. From this point of view, then, there seems to be but little choice of method, the one hour frog method probably giving the least range of variation in the testing of any *single* preparation of a simple nature, provided that it is soluble in water.

The second requirement of a method is that the results which it gives should be constant; that is, a given preparation should show approximately the same value when tested at different times and after long intervals if it does not itself undergo deterioration. If it does deteriorate, the method should give an index of this change. This is peculiarly true of the cat method, for with the most permanent preparation which we have, ouabain, we have been able to obtain a uniform value since 1909; the specimen used then still gives a cat unit within 5 per cent. of 0.1 mg. per kg. of animal. Similar experiences with other members of the group have already been mentioned, namely, the case of the German leaf A.

Some of the critics of this method state that, being a general toxic one it will not show deterioration in digitalis preparations, for the products of deterioration are likewise toxic and the activity may, therefore, remain unchanged, or even become increased. This is not the fact. Instance the old specimen of fluid extract of adonis which gave a cat unit of 895 mg., while a fresh specimen, of which we also had a sample of the powdered drug, gave a unit of about 100 mg. for the tincture and also for the leaf in the form of a fresh infusion. We have recently examined a preparation of squill, a fluid extract, which gave a cat unit of 561 mg. several years ago and which now gives about 1100 mg. as its unit. It is unnecessary to multiply the examples further to show that the cat method fully meets the second requirement.

The frog methods also accomplish this purpose to a certain extent, but a cause of inaccuracy and untrustworthiness in such

determinations lies in the variations in reaction between different batches of frogs and will be discussed later.

The extent to which the guineapig method may be expected to provide a similar means of comparison cannot as yet be definitely stated, but certain results obtained by Haskell would seem to show that seasonal variations in these animals are such that comparisons cannot be drawn between tests made at different times of year. In a period of five months a given specimen of ouabain was tested on these animals and the activity found varied from 0.000,000,28 to 0.000,000,52 gram per gram of pig. Such enormous variations are absolutely unknown in cats, and have never been reported in frogs, by whatever method tested.

The method should be as little subject to the influence of adventitious factors as possible. All, or nearly all, are agreed that frogs are very susceptible to the influence of such factors, and the warmest advocates of the frog as a test animal admit that size, sex, season, temperature, moisture, presence of eggs, region from which obtained, etc., may materially affect the reaction of the animal to the heart tonic group. Baker [12] has made a study of many of these factors and states that: "The results emphasize the necessity of using a preparation to standardize the frogs for each series of assays." This necessity is becoming generally recognized by most of the workers in this field and such standardization introduces certain factors of great detriment to the general applicability of the method to the entire digitalis series. This will be considered separately.

In addition to the factors already mentioned as influencing the results on frogs it is to be recalled that dilution of the drug has a marked influence on the result obtained. Hale emphasizes the importance of maintaining the concentration of the specimen to be tested within such limits that the fatal dose for a frog will be contained in one cubic centimeter of the solution. Focke [13] states that the degree of dilution in the case of the strophanthus preparations is very important, for, "a higher dilution results in a higher reaction value."

Guineapigs seem to be quite as susceptible to the influence of extraneous factors as are frogs. Thus, Vanderkleed found that these animals are very susceptible to changes in diet and ventilation, and that these factors very quickly impair the health of the pigs or

[12] A. J. PHARM.; 1912; 84; p. 247.

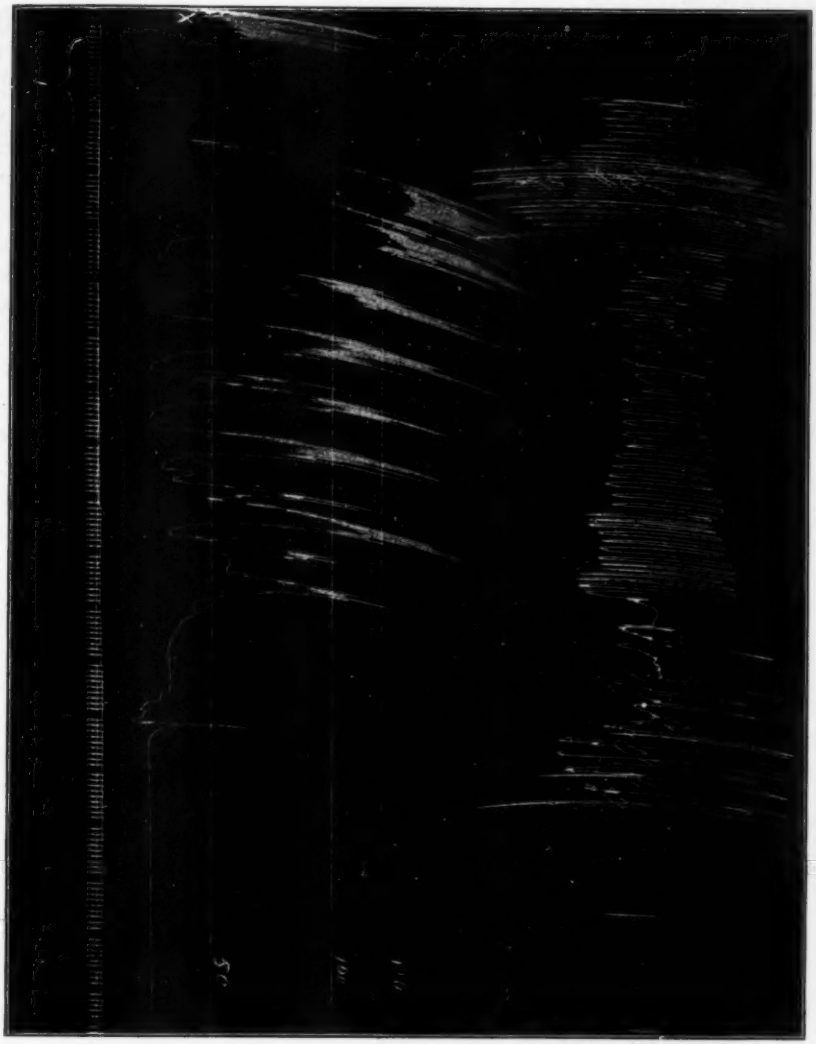
[13] *Arch. der Pharm.* 1910, 248, p. 345.

cause many of them to die. Haskell's observations on the seasonal variations in the reaction of guineapigs to a fixed drug, ouabain, show an enormous range of variation in response for different months. Thus, a series run in August gave the fatal dose, in terms of grams of the drug per gram of animal weight, as 0.000,000,28; in October the dose was 0.000,000,36; in November and December 0.000,000,52; in January 0.000,000,52+; in February 0.000,000,35 to 0.000,000,40; and in March it had come back to 0.000,000,36. From the lowest fatal dose of a series to the highest there is a difference of 0.000,000,24 gram per kilo of animal; that is about 100 per cent. of the lowest and 50 per cent of the highest. Haskell concludes, "From an examination of these tables, it is evident that in assaying a preparation of the digitalis group upon guineapigs a standard preparation is as necessary as is the case with frogs."

As is to be expected the cat method is also influenced by certain adventitious factors. Among those which have been brought up against it is the use of an anesthetic. This feature is one which we feel has given rise to a number of the great variations which some have reported from the use of this method, for it is not a difficult matter to kill a cat with an overdose of ether, and some of those who report these great variations have called attention to the fact that some of their animals died from respiratory failure. Such a mode of death is exceedingly uncommon in our experience, the heart practically invariably coming to a standstill before respiration fails, and while the respiratory center is still very active. This fact is confirmed by the observations made by Eckler, who found the heart to have stopped in nearly every case when the chest was opened at once after apparent death. Out of his 69 experiments he found the heart beating in only seven animals, "and in these the contractions were very feeble." The tracing shown was taken from the carotid artery and the trachea of a cat and shows the stoppage of the heart prior to that of respiration, and also partly explains the beating of the heart found in the seven cats reported by Eckler. This tracing is but one of a large number taken in this laboratory and represents the usual conditions of digitalis death.

Much stress has been laid upon the necessity for the continuance of an absolutely uniform grade of anesthesia during the course of the assay. In years of use of the cat method almost all of the possible changes have been rung on the grade and uniformity of the anesthesia and, short of killing the animal with the anesthetic, such variations seem to have little or no effect on the accuracy of

the method. A simple method of avoiding the dangers of the use of the volatile anesthetics is the substitution of one or another of



Tracing from the carotid-lower, and trachea-upper, at time of death from digitalis, cat. The points X correspond in point of time. Heart stopped suddenly six seconds after X, and respiration is seen to continue for more than a minute and a half, in fairly normal manner after brief stimulation. Bracket over I corresponds in time to bracket above respiratory tracing, and these oscillations in the pulse-curve seen to be attributable to the negative pressure in the heart due to increased inspiration, being synchronous with respiration. The group of rapid heart beats occur after the first stoppage lasting about twenty seconds, but these are never followed by permanent recovery of the heart.

fixed ones, such as chloral or paraldehyde. Experiments show that such substitution does not perceptibly influence the dose of the digitalis body required.

Food and drink has been stated to be a factor of great impor-

tance, especially in regard to the relation of the time of feeding or drinking to that of the testing. This can be made uniform and negligible by feeding at the same hour each day, the best time being late in the afternoon, thus leaving time for the complete digestion of food to have taken place before the animals are to be used for the tests on the following day. Food has also been shown to influence the reactions of frogs and guineapigs. Certainly the time of feeding will have as much effect upon the pigs as on the cats, for the influence is merely one of unknown alteration in the weight of the animals.

Sex influences the reactions of frogs, as has been shown (page 107), but *per se* it seems to have little or no influence on mammals. The occurrence of pregnancy or lactation on the part of cats does have a profound, and quite uncertain, effect upon the susceptibility of the animals, and we have seen variations from this cause of rather more than 50 per cent. in rare instances. Eckler reports the finding of one animal which took five times as much as the average, but in many hundreds of tests made in this laboratory we have never seen a tolerance even one-fourth so great as this. In view of the variability in pregnant and lactating cats they must, of course, not be used in biological assays.

We found that in one or two instances we could not secure the usual approximate uniformity in reaction between the individual animals of a series, even when using ouabain. All other possible factors being eliminated, it was suggested by Dr. Hatcher that the irregularity in response might be due to a seasonal variation in the susceptibility of cats. The animals seemed to be far less uniform in reaction in the summer months than at other times of year. Analysis of the records showed this to be the correct explanation, as is well illustrated in the table. Ouabain series A was made in the months of July and August and shows considerable lack of uniformity between the reactions of the several animals. Series B, on the other hand, was made in March and, with one exception, the variation between the individual animals is very slight.

This seasonal variation in cats is slight as compared with that shown to exist in guineapigs by Haskell (page 105). Even with the tendency to greater variation in the susceptibility of different cats during the summer months, it is possible to obtain results which very closely approximate the standard for a uniform preparation such as ouabain by the running of a small series of tests. This is shown by the series Ouabain A.

In none of the methods is it suggested that immature animals may be used along with mature ones, and one of Eckler's cats which showed marked abnormality of reaction was obviously a kitten, weighing only 970 grams. One of the first observations made by Hatcher on the factors which may enter to cause variations in the response of cats was the effect of an overabundance of fat (1) and this probably accounts for another of the great variations observed by Eckler, for one animal weighed 4.7 kg.

It is stated that frogs coming from different localities, although of the same species, show differences in reaction to the same preparation. Such does not seem to be the case with cats. We have established the cat unit for ouabain as 0.1 mg. per kg. and Eckler's table of 26 tests gives an average of 0.095 mg. per kg. A series of eight cats sent to us from Ithaca gave 0.093 mg. as the unit.

The fourth important requirement is that the method of standardization shall have a wide range of applicability, that is, it should be possible to use it for the evaluation of pure principles, galenical preparations, proprietaries, and unknown solutions containing one or more of the members of the digitalis group.

Both the guineapig and frog methods fail in greater or less degree to provide for such contingencies. In both the element of absorption is an essential factor and is the chief element which limits the range of applicability of these methods. Specimens which contain relatively large amounts of colloidal material would probably be found to give values considerably too low by the guineapig method, as colloids are well known to exert a marked inhibitory action upon absorption from the subcutaneous tissues. In the case of the frog methods this element of absorption is well illustrated by our utter inability to establish any fatal dose for liquid digalen by the one hour tests. Hale's determination which shows crystalline digitoxin to be, "eight times less active than amorphous strophanthin" is another illustration of the effect of absorption. Certainly no one believes that this ratio is in any way proportional to the relative activity of the two drugs for man or the higher animals.

High alcoholic content of the preparation renders it necessary to evaporate off the alcohol, at least in part, and make up the solution with saline for testing by the frog method, and the same process is followed by Reed and Vanderkleed in their tests of tinctures on guineapigs, although they state that the guineapig is very resistant to alcohol. The introduction of heat and the change of solvent are

capable of materially altering the activity of some of the digitalis preparations.

The cat method has neither of these disadvantages. The question of absorption does not enter, as the drug is introduced directly into the circulation. The alcoholic content of the preparation does not prevent its assay without evaporation unless it is extremely weak in cardiac activity, for the preparation is diluted for injection and the administration is so slow that the alcohol which is introduced never accumulates in the body to an extent sufficient to cause more than very slight cerebral depression. When the preparation is very highly alcoholic, or so weak that a relatively large volume of alcohol would have to be given, it is still unnecessary to remove any of the alcohol or to reduce the volume by evaporation, for the combined method with ouabain is readily applicable and gives equally good results. These statements are supported by the experiments cited in Table 2.

TABLE 2.

STANDARDIZATION OF LIQUID DIGALEN.

CAT METHOD.

Specimen	Dose in c.c. X kg.
A	1.86
	2.06
	1.94
B	2.00
	2.06
	2.03
C	1.57
	1.59
	1.17
	1.55
	1.74

ONE HOUR FROG METHOD—Specimem C.

Dose in c.c. X kg.	Result	Remarks
0.045	beating	incomplete absorption
0.045	systolic stand still	complete absorption
0.060	beating	incomplete absorption
0.060	beating	incomplete absorption
0.075	beating	incomplete absorption
0.075	systolic stand still	complete absorption

It is unnecessary to give a longer series of tests on frogs as no concordant results could be obtained by the method. Death in many of the other frogs used in which the dose was somewhere within the limits stated above, and where absorption was complete, was delayed much beyond the hour, or the heart was found beating feebly with the ventricles in a condition of mid-diastole; in still others the ventricles were found in complete diastole. The frogs were standardized against ouabain and reacted normally. All of them were between 20 and 30 grams in weight, and all were males and healthy.

Weis [14] experienced similar difficulty with the one hour frog method in testing liquid digalen, and found that glycerin in dilute solution retards absorption markedly. Tests which we made with crystalline digitoxin prepared in a menstruum similar to that of digalen showed a similar inhibitory action of the glycerin on absorption, with the result that the dose determined was much too high. The frog method is further unsuited for the testing of this preparation (Digalen) because the smallest dose which would kill the animals at all was more than one c.c. for a frog of average size, ranging up to 2.5 c.c. in some cases. In comparison with these results those obtained by the cat method are found to be very concordant and satisfactory. The greatest variation with specimen A is 5.6 per cent. of the average dose, and in B only 1.4 per cent., while in C one animal fell 23.0 per cent. below the average; with this latter discarded the maximum variation is only 8 per cent. of the average dose. It is interesting to note that digalen, which is said to consist of amorphous digitoxin, and which seemed so weak by tests on frogs, when used in the liquid preparation, was found to be very active on frogs when the tablets were used and the solution prepared without glycerin, whereas the tablets were found to be much weaker when tested on cats. This discrepancy is easily understood if we suppose that the rapid absorption of the glycerin-free solution hastens the action on the frog's heart.

Illustrating the applicability of the cat method to the testing of very highly alcoholic preparations the results obtained with two samples of fluid extract of adonis, tested by both the direct and the combined methods, may be cited. Together with this there is given an assay of the leaf from which one of the fluid extracts was

[14] Oest. Sanitaetswesen; Beilage zu No. 22, May 30, 1912.

made. One of the fluid extracts was made with 50 per cent., the other with 75 per cent. alcohol. The figures are given in Table 3.

TABLE 3.

STANDARDIZATION OF FLUIDEXTRACT ADONIS.

Specimen	Direct Method Dose in Mg. X kg.	Combined method Dose in Mg. X kg.
A	110, 130 } = 102	130, 98, 107 } = 111
B	100, 88 } = 94	105, 96 } = 100
Fresh Infusion of Specimen B.		
A	100, 93 } = 96.5	

In this series of standardizations there were but few tests and no special effort was made to obtain an exact evaluation in any case, as the purpose of the tests was merely to show whether there was any very great difference in the activity of preparations made with different strengths of alcohol, and a number of different samples were to be tested, coming from widely different sources.

The fifth consideration is that of providing a means of comparing widely different members of the group, both as regards their relative activity and with reference to their toxicity for man.

The elements introduced by the factors of absorption in the frog and guineapig methods limit the usefulness of these with regard to this last requisite. It is well known that even the so-called pure principles, and those which are the purest—ouabain and crystalline digitoxin—are entirely different in their absorbabilities from different tissues. Further, the relative activity of digitoxin and amorphous strophanthin as found by Hale on frogs is certainly no indication of the relative toxicity of these two drugs for man. Famulener and Lyons found strophanthin 17 times as toxic as crystalline digitoxin on frogs, but surely no one would venture to give a man 17 mg. of the latter by vein at a single dose, granted that it could be administered thus, yet if the method is to be of value as an indication of the probable activity of different digitalis bodies for man such a comparison should hold. Again, in testing the liquid preparation of digalen on frogs Hale found the most

active specimen to be 2.75 times weaker than crystalline digitoxin, while Weis also found the drug very much weaker than it is claimed to be. In contrast with these findings we were unable to fix the dose of the liquid preparation on frogs by the one hour method, but by extracting the amorphous digitoxin, so-called, from the tablets and using it in solution in saline we found that the fatal dose per gram of frog was 0.0085 mg., or that the drug is of equal activity to crystalline digitoxin. This finding compares well with the result of tests of the liquid preparation by the cat method, from which we found the most potent sample to be almost identical in activity with crystalline digitoxin.

It is evident from these illustrations, and from others which could be cited, that the frog method does not give results which can be transferred to man, in the matter of showing the relative activity of different preparations. This fact was early observed by Focke, the first to suggest the use of the frog and the strongest advocate of the frog methods. He says, "But the relative values for the different preparations, for example, Folia Digitalis Titrata and a so-called digitalis pure principle, found on frogs can never be transferred to man."

As to the possibilities offered by the guineapig method for the transference of the results to man, they are about the same as with the frog methods.

The cat method does, however, give results with practically all of the members of the series, which are strictly conformable to the relative activities of the several members for man. Thus, ouabain is nearly twice as active on man as is the average specimen of amorphous strophanthin, and is 1.75 times as active on the cat. Of course it is to be understood that this comparison is between the intravenous doses in both instances, though in both man and cat these two drugs show a similar tendency to great irregularities in rate and degree of absorption from the gastro-intestinal tract.

It has been suggested that, to make allowances for the variabilities found in frogs from one cause or another, each batch be standardized against some uniform and constant preparation. Impurities, variation in strength of different samples of many of the isolated glucosides, and the uncertain keeping qualities of the crude drugs and galenical preparations have limited the choice of the drugs for this purpose to either ouabain or crystalline digitoxin. In view of the profound influence of rate of absorption on the results obtained by the frog tests, the establishment of the reaction

of a batch of these animals to either of the "standard" drugs, or even to both of them, does not necessarily give any index of their reactivity toward other members of the digitalis series. It does not even suffice for the testing of digitalis itself to standardize the frogs against digitoxin, for it is generally believed that digitalis owes its activity to other glucosides in addition to its digitoxin content, and that the relative amounts of the several glucosides present is not constant, or the same for any two samples.

The necessity for the similar standardization of the guineapig prior to each series of assays has been urged by Haskell, but it is obvious from the enormous seasonal variations found to exist in these animals that no standard reaction can be obtained, and absorption plays a part here as well as in the case of frogs.

The method of assay should be one which tests that action of the drug upon which its therapeutic use depends. One method does this as well as another, for each depends upon the production of death through the action of the drug upon the heart. Upon this point several have raised objections to the so-called general toxic methods on the cat and guineapig. These objections are not valid for it can be shown that death by either of these methods is due to paralysis of the heart. Reed and Vanderkleed and Githens and Vanderkleed hold this to be true for the guineapig method, and the action in the cat method has been shown to be upon the heart, a point confirmed by the observations of Eckler already cited. The tracing reproduced on page 109 illustrates the truth of this statement, and we have taken a very large number of such tracings, all of which give the same evidence, namely, that death is primarily due to cardiac paralysis, though in some rare instances the heart becomes so weak just prior to its cessation that the circulation is insufficient to maintain a completely normal state of the respiratory center, and these animals show dyspnea and sometimes, even, temporary stoppage of respiration. A further fact which shows that death in the cat is not due to the action of the drug on the respiratory center is that artificial respiration does not alter the dose which is required to cause death, an observation frequently made by us and one which is strikingly shown by the experiments which Eckler made. He found that at most the induction of artificial respiration permitted the injection of an additional c.c. of the ouabain solution, truly an insignificant amount (0.01 mg.) for a cat of several kilos. It might also be mentioned that drugs which act directly and chiefly on the respiratory center to produce death cannot be

standardized by biological methods, if death be made the end reaction, on account of the great variability in the reactivity of this central nervous mechanism, at least quantitatively.

The factors of minor importance in the choice of the method for biological standardization of the digitalis bodies are several. The first, and the one which has been invoked against the cat method most often, is the matter of difficulty. The frog methods are very simple in so far as the mere injection is concerned but it requires the exercise of considerable judgment and experience, not to say some knowledge of physiology, to determine exactly when the ventricles may be said to have just come to systolic standstill, and such accurate determination is essential in the one hour frog method. Again, the quantities of the solutions which are used for frogs are so small, and the dilutions relatively so great, that very slight inaccuracy in measurements or in the calibration of instruments are likely to lead to gross variations in the results, which are, at least, confusing to the observer.

The guineapig method is probably the simplest of all of the methods advocated, but its other disadvantages are such as to make it unlikely of adoption.

The cat method is less simple in technique than the others, but it is not so difficult as its critics would have us believe. First, it is said to be very difficult to insert a cannula into the vein of an anæsthetized cat. Our laboratory boys perform this operation readily, and we find that our students experience no great difficulty in learning this simple procedure after only one or two trials.

The question of the maintenance of anesthesia has already been discussed.

The duration of the rate of injection is another stumbling block for our critics. They tend to "make a mountain out of a mole hill" in this matter, for it is really quite simple, with a very limited experience or by reference to previous results, to estimate with reasonable accuracy how rapidly the injection of any given digitalis preparation should be given. For example, if the operator has a tincture of digitalis of unknown strength to test, he may assume that it is of about the average activity, for most tinctures approximate the average. By reference to previous tests he can find that a rough average to be expected would be about 100 mg. per kg. of animal. By diluting the tincture with nine volumes of saline solution he then makes each ten cubic centimetres contain about the expected dose, he then has but to multiply the weight of the cat in

kg. by ten and divide by ninety, the theoretically appropriate duration of the injection in minutes, and the resulting figure will be the number of c.c. to be injected per minute. But as we are dealing with an estimated activity of 100 mg. per kg. it is not necessary to go through this elaborate calculation, for the multiplication by 100 at first is about neutralized by the subsequent division of the result by ninety, so that he has merely to inject a number of c.c. per minute equal to one-tenth of the weight of the cat in kg.

After all of this discourse on the exact or approximate estimation of the time of the injection and its rate, I would say that in the years during which the method has been in use in this laboratory injections have been made over periods varying from ten minutes to three or four hours and, save for the likelihood of "running over" in the case of the shorter period, the duration has shown little or no appreciable effect upon the ultimate dose required. It is not to be understood, however, that such wide differences are advocated, they are merely mentioned to show that great nicety in the estimation of the rate of injection is quite unnecessary. All that is required is that the injection shall be slow enough to reduce the likelihood of greatly exceeding the minimum fatal dose and rapid enough to avoid such theoretical factors as the possible excretion of some of the drug or of seriously injuring the heart through prolonged anesthesia. Injections lasting 6 hours have given results somewhat too high.

The cat method has been said to be so time consuming that it is impossible to make a standardization of more than one specimen in a single day. The following is an answer to this contention:

Eight cats were obtained from Ithaca, N. Y., for the sake of testing the reaction of animals from outside of the city.

At 9.00 A.M. the laboratory helper began to weigh the animals and prepare burettes, boards, instruments, etc., for their testing. At the same time an accurate solution of ouabain was prepared. When these preliminaries, including the filling of the 8 burettes, were completed an animal was etherized and tied to a board. While the operator was exposing the femoral vein and inserting the cannula connected with the burette a second cat was being etherized and by the time it had been tied on a board the first injection had been started and a record made of the time on the slip on which the boy had written the weight and description of the animal. In this manner all of the 8 animals were prepared and the injection begun in each, with an average of 7 minutes needed for the com-

plete preparation of each of the animals. It was a very simple matter for the operator, aided by the laboratory boy, to administer a few drops of ether from time to time as the individual animals required, and at the same time to watch and control the rate of the several injections. The results are given in Table 4.

TABLE 4.

STANDARDIZATION OF ITHACA CATS.

Cat	Sex	Weight in Kg.	Duration of injection in minutes	Dose of ouabain Mg. X Kg.
1	f	2.04	72	0.09
2	f	2.38	72	0.09
3	f	2.00	84	0.09
4	m	4.32	71	0.085
5	f	1.47	74	0.098
6	m	1.61	92	0.099
7	f	2.20	83	0.084
8	f	1.44	52	0.110

The total time consumed in the estimations on these 8 cats from the beginning of the first anesthesia to the death of the last animal was one hour and fifty-seven minutes and no special effort was made in the matter of haste. The average duration of injection was 75 minutes and the average dose of ouabain required was 0.093 mg. per kg. of cat weight, a figure only 7 per cent. below the established cat unit. The greatest variation from the average is 18.2 per cent. above, and this was obtained from the only animal which did not seem quite normal before the tests were begun, being considerably depressed and not at all lively or vigorous.

The last animal died at 12.12 P.M., three hours after preparations were begun for the tests, another 20 minutes was required for the calculation of the doses taken by the animals. Three hours and a half may be taken as the extreme limit of time needed for this series of 8 tests.

How does this compare with the other methods as regards the element of time required? The twelve hour frog method, obviously, cannot be done in less than twelve hours. The one hour frog method would require at least 15 minutes for the preparation of the solution and the weighing of the frogs, together with their injection. It usually requires the use of at least three groups of frogs for an accurate determination, each group requiring one hour, the total time for an assay would then scarcely fall within less than three hours and a half.

The guineapig method at best requires an entire day, and Hale found that it often consumed two days for a single assay.

The methods are all humane hence this point needs no comment.

The last minor matter is that of expense. Frogs are the cheapest of the animals but they are prone to die from epidemics of the "red leg disease," and a large number of each consignment is usually female, and most of these are rendered useless by the presence of large masses of eggs, so that it is not probable that an assay by these animals could be done at a cost of less than 50 to 75 cents. Hale found that the guineapig method cost from $2 to $5.50 per assay. In New York City cats cost ten cents each, but in other cities and towns they are more expensive, some reporting that they cost as much as guineapigs. If the factor of cost is so important it would certainly be quite as possible for the large manufacturing houses to breed cats as it is guineapigs, and probably at considerably less cost than in the case of the latter, for their food is cheaper and they do not eat so much. The cat method was originally proposed as one which would be available for the small manufacturer or the retail pharmacist and it would certainly seem that it is still the preferable method for this purpose as it is always a simple matter to secure four to six cats at a small cost and without much trouble, whereas the purchase and keeping of guineapigs and frogs is expensive and troublesome, and the care of both of these animals requires special facilities. Both are liable to destruction by unavoidable factors, frogs by drying, and the "red leg disease," guineapigs by improper food, exposure to draughts, epidemic diseases, and one instance might be mentioned when a large number of these animals were killed in a single night by the invasion of a common rat.

SUMMARY.

1. The frog methods are the cheapest of all.

2. The one hour frog method and the cat method require about the same length of time and are much less time consuming than the guineapig or twelve-hour frog methods.

3. All four methods are humane, there being no preference on this point.

4. The guineapig method is by far the simplest, both of the frog methods and the cat assays requiring some experience and skill.

5. All of the methods test the cardiac action of the specimen, but, other things being equal, those on the higher animals are to

be preferred on account of the greater similarity between these and man; this being especially characteristic of the cat method.

6. The results of the frog methods cannot be transferred to man, not even the results of tests of the relative toxicity of different closely allied bodies. The standing of the guineapig method on this point is much the same. The cat method does give results which are directly transferable to man, both as regards actual toxicity of a single drug and the relative activity of different members of the series.

7. It is not possible to compare different members of the digitalis group by the guineapig or frog methods, owing, principally, to the great influence of absorption on the results obtained by these methods. By the cat method comparisons can be made of the activity of any two or more members of the series wholly regardless of their differences in absorbability.

8. The frog and guineapig methods are limited in their range of applicability by factors of absorption, alcoholic content, etc. This is not the case with the cat method, which has a wide range of applicability.

9. All of the methods are subject to the influence of adventitious factors, the guineapig method being the most affected, the frog the next, and the cat the least. In the latter animal the use of a short series of tests practically nullifies the influence of the adventitious factors.

10. The frog and guineapig methods show moderate to great differences in the evaluations made for the same specimen at different times, and hence cannot be trusted to give correct information concerning the presence or absence of deterioration in a given preparation. The cat method gives concordant results with permanent preparations tested at long intervals and shows the presence of deterioration with certainty.

11. It is possible to obtain reasonably accurate results with any of the methods—to within ten per cent.—but the frog method probably gives the least range of variation in the case of a pure principle, provided that it is soluble in water.

12. The cat method is the only one which affords any evidence of the relative therapeutic value of the different members of the digitalis group.

CONCLUSIONS.

There is no perfect or ideal method of standardizing the members of the digitalis group biologically.

Each of the four methods discussed—the one and twelve-hour frog methods, the guineapig, and cat methods—has certain advantages not possessed by the others.

The method which possesses the greatest number of advantages is the cat method of Hatcher—

(*a*) It is accurate to within ten per cent.

(*b*) It gives constant results from year to year.

(*c*) It provides a means of detecting the presence of deterioration.

(*d*) It is the least affected by adventitious factors.

(*e*) It tests the action of the drug upon which its therapeutic use depends.

(*f*) It is not too difficult for general use.

(*g*) It is neither too time consuming nor too costly.

(*h*) By it widely different preparations can be compared accurately.

(*i*) Its results are transferable to man.

(*j*) It has the widest range of applicability of all the methods.

Neither the frog nor the guineapig method fulfils so many of the essential requirements as does the cat method.

The cat method fails in no single requisite and has far fewer disadvantages than any other method yet proposed.

PROGRESS IN PHARMACY.

A Quarterly Review of Some of the More Interesting Literature Relating to Pharmacy and Materia Medica.

By M. I. Wilbert, Washington, D. C.

An unusual amount of interest is being manifested in the prospective legislation on matters relating to public health and not the least among these several subjects is the legislation designed to effect, either directly or indirectly, the practice of pharmacy. From 38 to 40 of the state legislatures are now in session and in the majority of these bodies some form of legislation more or less directly affecting the practice of pharmacy is being considered.

Legislation designed to further regulate the manufacture and sale of habit forming drugs is being endorsed by physicians and pharmacists generally because of the general appreciation of the

need for restrictions of this kind, from a public health point of view, and also because of a natural desire to refute, in a definite and positive way, the repeatedly made claims that medicine and pharmacy, individually or collectively, are at fault in fostering the illegitimate or unnecessary spread of the habitual use of narcotic drugs.

Among the measures that have been introduced to further regulate the sale of drugs of this type no one is of more immediate interest than the bill recently introduced into the House of Representatives by Mr. Harrison, of New York, and generally designated as H. R. 28,277. This bill is in effect a substitute for a previously introduced bill, H. R. 28,023 and contains several features endorsed by representatives of the various National drug associations that recently held a meeting in the City of Washington. The importance of this measure is emphasized by the fact that it is designed to provide a readily available record of all purchases and sales of habit forming drugs and thus to facilitate the enforcement of existing State laws.

The National Drug Trade Conference.—This is the name under which representatives of the American Pharmaceutical Association, The National Association of Retail Druggists, the National Wholesale Druggists' Association, the National Association of Manufacturers of Medicinal Products and the National Association of Pharmaceutical Chemists organized, in the City of Washington, on January 15, 1913, a permanent legislative conference.

The prime object of this conference is to endorse and endeavor to secure greater uniformity in the several State and Federal laws relating to the manufacture and distribution of drugs and medicines of all kinds. The following resolution was adopted as being expressive of the object of the conference:

The National Drug Trade Conference in session in Washington this 15th day of January, 1913, herewith submit by unanimous resolution that this conference is heartily in favor of Federal Legislation of such a nature as to bring under control the importation and the interstate traffic in so-called habit-forming drugs in such a measure as to prevent their illegitimate use without placing unnecessary burdens upon the manufacturer, jobber, retailer, or physician.

Publicity and the Practice of Medicine.—An editorial (*J. Am.*

M. Assoc., 1913, v. 60, p. 375) in commenting on the inevitable requirement for greater publicity in connection with the practice of medicine says: "The American public has already awakened to the fact that the prescribing of fraudulent or unscientific proprietary mixtures by physicians is an evil but one degree removed from that of self dosing with patent medicines. The sooner the medical profession realizes this the better it will be for its own dignity and scientific standing.

Proprietary Medicines.—In England the Select Committee on Patent Medicines is still collecting evidence for and against the continuance of privileges accorded to this class of medicinal preparations. A report (*Chem. and Drug.*, 1913, v. 82, p. 54) of the session held on January 23 is not particularly inspiring and should go far to convince the members of the committee that the methods and the ideals of at least many manufacturers of patent medicines are not designed to further the best interests of the public.

Classification of Medical Colleges.—The Council on Medical Education (*J. Am. M. Assoc.*, 1913, v. 60, pp. 231–234) presents the third classification of the medical colleges of the United States with an outline of the basis on which the classification was made. While it is true that considerable opposition has been encountered to the work of the Council the rapidly growing list of class A schools evidences the fact that the work of the Council on Medical Education has been productive of good results and that the whole plane of medical education in this country has been and is being rapidly raised. From a pharmaceutical point of view the results that have been attained should not, and in effect cannot be ignored as it is but a matter of time when pharmaceutical schools will be measured by the achievements that have been recorded for medical schools.

Ph. Germ. V.—Taub, L. (*Ztschr. f. ang. Chem., Pharm. Ztg.*, 1912, v. 57, p. 886), in a comprehensive review of the evolution of the Prussian and succeeding German Pharmacopœias presents tables showing the date of publication and the number of titles contained in these several books. The first edition of the Prussian Pharmacopœia, published in 1799, is reported to have contained a total of 685 titles, while the now official pharmacopœia contains 638 titles. The maximum number of titles was reached by the Ph. Germ. I, published in 1872, which contained 896 titles. This

was reduced, however, in the Ph. Germ. II to 592, while the edition of the German Pharmacopœia published in 1890 contained the least number of titles reported: 591.

Ph. Brit.—Sir Donald MacAlister, the president of the General Medical Council of Great Britain, in a recent address stated that the Pharmacopœia Committee with the help of its editors had prepared for the press the draft of four large sections of the text for the new British Pharmacopœia. It was hoped that the first proofs might be ready for submission to the committee early in the new year, and that thereafter the work that still remained to be done would be rapidly advanced. (*Brit. and Col. Drug.*, 1912, v. 62, p. 467.)

Ph. Belg. III.—The Journal de Pharmacie d'Anvers (1912, v. 68, pp. 646–670) reprints the proposed supplement to the Ph. Belg. III prepared by the permanent pharmacopœia commission. The descriptions are provisionally offered so that pharmacists may have an opportunity to present criticisms. The provisional text includes descriptions for 28 articles; 18 chemicals, 9 preparations and 1 drug, coca.

Brussels Conference.—A reply to a query (*J. Am. M. Assoc.*, 1912, v. 59, p. 2175) calls renewed attention to the Brussels Conference and the international treaty on uniformity of pharmacopœial formulæ for potent medicaments and points out that in practically all of the Countries of Europe where the National Pharmacopœias have been revised, the provisions of the treaty have been closely adhered to. The total number of compliances with article 1 of the original protocol has been increased from 129 in 1902 to 260 in 1910, while the non-compliances have been reduced from 131 in 1902 to 15 in 1910; the present U. S. P. being responsible for no less than 5 of the latter.

Light and Drugs.—An editorial (*J. Am. Med. Assoc.*, 1912, v. 59, p. 2160) calls attention to the observations of Neuberg, who found that nearly all types of organic compounds acquire a pronounced photosensitiveness when they are mixed with certain inorganic compounds. Iron salts, for instance, provoke this effect most strikingly; and the phenomena of change induced by the presence of such sensitizing substances fail to evince themselves so long as the solutions containing them are kept in the dark. Many familiar drug preparations represent combinations of organic com-

pounds and metallic elements and the obvious outcome of the observations so far recorded by Neuberg and others is that preparations containing metallic components should be preserved in dry form if possible and in any event they should be kept in dark containers and protected against light.

Outline of Micro-analytical Methods for Food and Drugs Laboratories.—Schneider, Albert (*J. Am. Pharm. Assoc.*, 1912, v. 1, pp. 1330–1338) discusses the value of the compound microscope as a ready means for determining the identity, quality and purity of foods and drugs, and outlines the methods of procedure.

Some Commercial Samples of Drugs.—Linton, A. W. (*J. Am. Pharm. Assoc.*, 1913, v. 2, pp. 30–35), reports the examination of a number of samples of asafetida, ammoniac, myrrh, gamboge, guaiac, benzoin and lycopodium and concludes that ash standards might well be established for an additional number of drugs, other than those for which they are at present stated, but a method of procedure should be outlined.

The Alcohol Requirement of the Pure Food and Drug Law and the Accuracy of Alcohol Assays of Pharmaceutical Preparations.—C. H. Briggs. (*J. Ind. Eng. Chem.*, 1913, v. 5, pp. 29–30.)—In the making of alcohol assays there are several sources of error and the result may be off 1 per cent. or 1.5 per cent. alcohol. Briggs believes that a ruling to the effect that fluid extracts and elixirs could be labelled with maximum content of alcohol would be just and fair and would not in any way deflect the real intent of the Drug Law.

Wood Alcohol Poisoning.—Casey A. Wood (*J. Am. M. Assoc.*, 1912, v. 59, pp. 1962–1966) calls renewed attention to the danger of death and blindness from wood alcohol poisoning and points out that 30 years ago poisoning from wood alcohol was practically unknown. With the elimination of the disgusting odor and vile taste of the preparation as then known and the introduction of the refined product, under various trade names, the preparation began to have more extended use and was freely advertised as a harmless and efficient substitute for grain alcohol, and is even now, freely sold in drug stores not infrequently to the exclusion of the less objectionable denatured alcohol.

Asafetida.—An editorial (*Chem. and Drug.*, 1912, v. 81, p. 51) states that the continued rejection of asafetida by the United States

Customs is causing considerable trouble on the London market and the drug has the reputation of being the most difficult to handle so far as imports into the United States are concerned. It is now proposed to accept asafetida on the basis of a lead number, the equivalent of the amount of metallic lead, in milligrams that is used up by a 1 gram sample of ether purified resin.

The lead numbers obtained from various resinous products, according to Merrill are: Asafetida, 222; galbanum, 4; ammoniacum, 75; olibanum, 0; guaiacum, 171; myrrh, 7; colophony, 142; sandarac, 351; mastic, 34; gamboge, 9.

Ernest J. Parry.—(*Chem. and Drug.*, 1913, v. 83, p. 180.) Condemns the proposed "lead value" for the ether soluble resin of asafetida and expresses the belief that there is no authority for assuming that 220 or thereabouts represents even the approximate value of genuine asafetida. Reports on 5 samples vary from 144 to 172 and the suggestion is made that in the event that a lead number of 200 be insisted on no dealer will venture to ship asafetida to the United States.

Buchus.—Harold R. Jensen (*Pharm. J.*, 1913, v. 90, pp. 60–61) reports a comparative study of *Barosma venusta* and of *B. betulina* and *B. serratifolia* and concludes that neither the leaf nor the oil of the former can be expected to clinically replace either of the latter varieties of Barosma.

Calcium Glycerophosphate.—The Council on Pharmacy and Chemistry (*J. Am. M. Assoc.*, 1913, v. 60, p. 45) describes Calcium glycerophosphate as the monohydrated normal calcium salt of glycerophosphoric acid, containing not less than 90 per cent. of anhydrous calcium glycerophosphate. It occurs as a fine white powder, odorless and almost tasteless; somewhat hygroscopic, slightly soluble in water and almost insoluble in hot water and insoluble in alcohol or ether. An aqueous solution is alkaline to litmus paper.

Caulophyllum.—Power and Salway (*Chem. and Drug.*, 1913, v. 82, pp. 202–203). *Caulophyllum thalictroides* was found to contain two crystalline glucosides possessing the character of Saponins. The glucoside occurring in predominating amounts is identical with Lloyds "Leontin" but as it has now been more fully studied the name caulosaponin is proposed for this product and caulophyllosaponin for the accompanying glucoside.

Cresol Preparations.—Raschig, F. (*Südd. Apoth.-Ztg.*, 1912, v. 52, p. 670), states that J. Schenkel was the first to discover the crude tar distillates, containing approximately 33 per cent. of phenols, could be made miscible with water by the addition of rosin soap. Schenkel marketed a preparation of this kind under the name "Sapokarbol II." This was subsequently imitated by other manufacturers and under the name "Creolin" or "sheep-dip" has found a widespread application and for some purposes it is claimed to be more efficient than the corresponding soap solution of cresol.

Cycloform.—Is the name applied to isobutyl para-aminobenzoate or para-aminobenzoic acid isobutyl ester. It occurs as a fine white, crystalline, odorless powder that is soluble in ether, benzol, acetone, alcohol and olive oil but is only slightly soluble in water. It melts at 65°. Cycloform acts on wound surfaces and mucous membranes as a superficial and prolonged anæsthetic and as a mild antiseptic. (*J. Am. Med. Assoc.*, 1912, v. 59, p. 2150.)

Digitalis Preparations and Some of the New Substitutes for them.—An editorial (*J. Am. Med. Assoc.*, 1912, v. 59, pp. 2074–2075) calls attention to a report from the Pharmacological Laboratories at Cambridge, England, which reiterates the frequently made statement that so far not one of the new, generally proprietary, preparations of digitalis has made a successful bid for superiority over an active tincture of digitalis. (See also *Ibid.*, 1913, v. 60, p. 143.)

Digitalis.—Hatcher and Eggleston (*J. Am. M. Assoc.*, 1913, v. 60, pp. 499–503) report a study of the relative emetic and cardiac activities of the more commonly used digitalis bodies in which they call attention to their previously reported observation that the emesis sometimes produced by digitalis bodies is due mainly, if not entirely to the action on the vomiting center in the medulla and conclude that we at present have no means of securing the cardiac action of the digitalis bodies without subjecting the vomiting center to their influence at the same time. (See also *Ibid.*, p. 371.)

Elarson.—A new arsenic preparation containing strontium and chlorine, occurs as a nearly colorless and odorless amorphous powder, insoluble in water but slightly soluble in alcohol, ether and fatty oils. Elarson contains 13 per cent. arsenic and 6 per cent. chlorine. (*Suedd. Apoth. Ztg.*, 1913, v. 53, p. 20.)

Epinephrine from the Whale.—An editorial (*J. Am. M. Assoc.*, 1912, v. 59, p. 2263) calls attention to a paper by Weidlein on the adrenal glands of the whale, which were found to be about five hundred times as large as the corresponding glands of sheep and fifty times as large as the glands from cattle. The yield of epinephrine is proportional to that hitherto obtained from other animals, so that as much as 1.2 gm. of the typical active principle has been isolated from a single whale adrenal gland.

Glycerin.—An editorial (*Chem. and Drug.*, 1912, v. 81, p. 752) states that the chief use for glycerin is in the manufacture of dynamite for explosive purposes. Among the rapidly developing uses for high explosives not the least important is its use for ploughing.

Glycotauro is the name applied to a purified ox bile standardized to contain 50 per cent. of bile salts free from bile pigments. Each 1 gm. represents approximately 10 c.c. of fresh ox bile. Glycotauro occurs as a soft, semi-solid mass of light brown color, bile-like odor and slightly bitterish taste. It is readily soluble in water and in alcohol. (*J. Am. Med. Assoc.*, 1912, v. 59, p. 2066.)

Hediosit is the lactone or inner anhydride of alpha-glucoheptonic acid. It is prepared by treating glucose with hydrocyanic acid the condensation product being treated with barium hydroxide and the lactone of alpha-glucoheptonic acid liberated by the addition of sulphuric acid. Hediosit is a white, crystalline, odorless powder possessing a sweet taste, it is readily soluble in water, slightly soluble in alcohol and almost insoluble in ether. The aqueous solution is acid toward litmus. It is said not to be poisonous and is given in doses of from 10 to 30 gm. (*J. Am. M. Assoc.*, 1913, v. 60, p. 516.)

Heroin, Facts About.—An editorial (*J. Am. M. Assoc.*, 1912, v. 59, pp. 2262–2263) points out that although heroin and its hydrochloride have been in use but a few years, they have already established themselves among the habit forming drugs and have become sufficiently conspicuous in this respect to awaken the thinking public to the deplorable results for which they may become responsible. See also article by John Philips, *Ibid.*, 1912, v. 59, pp. 2146–2147.

Hexal is the name applied to hexamethylenamine salicylsulphonic acid. It is prepared by the interaction of an alcoholic solution of salicylsulphonic acid and an aqueous solution of hexa-

methylenamine. Hexal occurs as a white, odorless crystalline powder, readily soluble in water, slightly soluble in alcohol and difficultly soluble in ether. It is claimed that hexal has the action of hexamethylenamine combined with an anæsthetic and astringent action due to the salicylsulphonic acid. It is given in doses 1 gm. (15 grains) three to six times a day. (*J. Am. M. Assoc.*, 1912, v. 59, p. 1971.)

Ipecac in Dystentery.—Harvey G. Beck (*J. Am. M. Assoc.*, 1912, v. 59, pp. 2110–2114) reports a review of some of the literature on the treatment of dysentery by means of ipecac and reports a number of cases to show that ipecac when administered through a duodenal tube is distinctly more efficacious than when administered in any other way.

Isatophan is methoxy-atophan and occurs as a lemon-yellow crystalline powder melting at 216°. It is soluble in alcohol and alkalies but insoluble in water or ether. It is practically tasteless but possesses a slight odor resembling atophan. (*J. Am. M. Assoc.*, 1913, v. 60, p. 516.)

Neosalvarsan.—P. Ehrlich is reported as stating that at the present time it is not possible to decide whether neosalvarsan is to be given the preference over salvarsan or not. Exposed to the air neosalvarsan is more readily decomposed and the oxidation products appear to be even more toxic than are those of salvarsan. The untoward results that have been reported in connection with salvarsan Ehrlich attributes to the use of impure water, or distilled water that has been kept in lead containing glass vessels. (*Pharm. Zentralh.*, 1912, v. 53, p. 1220.)

Novatophan is described by the Council on Pharmacy and Chemistry as the ethyl ester of paratophan. It occurs as a slightly yellow, odorless and tasteless, crystalline powder that melts at 76° and is insoluble in water but readily soluble in alkalies, hot alcohol and strong acids. Its uses and doses are the same as atophan. (*J. Am. Med. Assoc.*, 1912, p. 59, p. 1971.)

Oil of Theobroma, Adulterations of.—Duyk (*Ann. chim. anal.*, 1912, v. 17, pp. 405–407) states that cacao butter is very frequently adulterated with other fats, the fraudulent additions being chiefly butter of cocoa nut, and less frequently green butter, the butter of Dika and of Illipé, wax, spermaceti, margarine and paraffine.

Primula Dermatitis.—H. A. Sharpe (*J. Am. M. Assoc.*, 1912,

v. 59, pp. 2148–2149) reports 4 cases of primrose dermatitis caused by the flowers of the wild primrose, *Primula farinosa,* Linné, which grows wild throughout the southern part of Wisconsin, Minnesota, Michigan and northern Illinois.

Salicylates, Relative Value of Natural and Synthetic.—Cary Eggleston (*J. Am. M. Assoc.,* 1912, v. 59, pp. 2057–2064) reports a comprehensive study of the literature on the relative toxicity of natural and of synthetic salicylates in an effort to locate definitely the reasons for the belief if reasons are to be found. He presents rather a comprehensive reflection of the literature and concludes that the evidence in favor of the "natural" salicylates is extremely slight, the bulk of the evidence indicating that physicians all over the world have demonstrated the artificial salicylates to be quite as effective as the "natural" and no more liable to produce unfavorable actions under similar conditions.

Salvarsan Solutions.—Adolf Jaiser (*Südd. Apoth. Ztg.,* 1912, v. 52, p. 726). The occurrence of thromboses following the intravenous injection of solutions of salvarsan prompted an inquiry which revealed the fact that the manufacturers have revised their system of control numbers so that it is no longer possible to distinguish the comparative date of manufacture. It was also observed that the physical properties of different samples of salvarsan varied widely.

Sodium Glycerophosphate.—The Council on Pharmacy and Chemistry (*J. Am. M. Assoc.,* 1913, v. 60, p. 442) describes sodium glycerophosphate as occurring in white monoclinic plates or scales, having a saline taste; odorless; easily soluble in cold and hot water; nearly insoluble in alcohol and containing not less than 99 per cent. of hydrated sodium glycerophosphate, with 5.5 molecules of water of crystallization.

Solidified Fixed Oils.—Aufrecht (*Pharm. Ztg.,* 1912, v. 57, pp 876–877) discusses the several processes of hydration that are being employed and points out that the most satisfactory results appear to have been obtained by catalytic processes, using nickel and palladium as the catalizing agents. While any fixed oil can be used, sesame oil, peanut oil, cottonseed oil, and castor oil have been experimented with most extensively. The chemical changes brought about are evidently due to the hydration of the unsaturated fatty acids, the iodine number being reduced to 3.9 per cent. cor-

responding to approximately 4.4 per cent. of oleic acid. The specific gravity of hydrated oil varies from 0.9252 to 0.9268 at 15° C. The melting point varies from 44.5° to 46.5° and the fat is readily saponified on boiling with alkalies.

Sulphuric Acid Caustic Pastes.—Pussey, W. A. (*J. Am. M. Assoc.*, 1913, v. 60, pp. 434–435), discusses the use and the formulas of sulphuric acid caustic pastes and notes that while a sulphuric acid paste may be effectively used for destroying lesions in the skin it is not a desirable agent when one needs to consider cosmetic effects. See also p. 462.

Thyroid Gland Preparations.—An editorial (*J. Am. M. Assoc.*, 1912, v. 59, p. 1980) notes that the products available in the form of desiccated thyroid are derived from several of the slaughter house animals, notably sheep, and the commercial preparations are frequently standardized in terms of their content of iodine. The glands of hogs are usually richest in iodine and their selection for therapeutic purposes appears decidedly rational, at least, so far as known, there is no occasion to reject the hog products.

Vanadium Preparations.—The Council on Pharmacy and Chemistry (*J. Am. M. Assoc.*, 1913, v. 60, p. 225) reports on a number of proprietary preparations containing vanadium and concludes that the manufacturer of these preparations has not submitted reliable evidence to substantiate the therapeutic claims that are being made for them. While vanadium itself may possibly have uses in medicine such uses, up to the present time at least, have not been firmly established.

THE MICROSCOPICAL EXAMINATION OF VEGETABLE PRODUCTS AS AN ADJUNCT TO THEIR CHEMICAL ANALYSIS.[1]

By A. L. Winton.

U. S. Food and Drug Inspection Laboratory, Chicago, Ill.

In solving the problems of man and nature the analytical chemist too often limits himself to chemical or physico-chemical methods. He is an analytical chemist in the strict sense of the word and not an analyst, which implies a man of broader training and experience,

[1] Reprinted from original communications, Eighth International Congress of Applied Chemistry. Vol. xviii, pp. 361-366.

utilizing the principles of other sciences as means to his end. He turns his back on the methods of vegetable and animal histology, physiology and bacteriology, asserting with satisfaction that he is a specialist and as such must limit his field of activity.

This attitude of the analytical chemist may be traced to a misapprehension as to the province of a specialist. Such a worker must be limited only in the field of application and not in training or the methods employed. An oculist, for example, limits himself to defects of vision and diseases of the eye and allied organs, but in order to properly carry out the work of his specialty he must have broad medical training and be conversant with the general principles of optics, bacteriology, chemistry and perhaps other sciences. Specialists in other sciences, both pure and applied, must also have good general training if they are to achieve distinction in their limited fields; otherwise they are in much the same position as the mechanic who, instead of mastering his trade, learns to operate one machine, thus becoming a mere automaton.

Botany and chemistry are generally considered incompatibles. The student of chemistry sometimes takes up bacteriology as a minor subject, but comparatively seldom studies advanced botany, even though he intends to specialize in food analysis, textile chemistry, paper technology or some other subject dealing chiefly with materials of vegetable origin. No physiological chemist would think of pursuing his investigation of animal materials without a working knowledge of animal anatomy, yet agricultural and food analysts and others dealing with vegetable materials too often limit themselves to a knowledge of chemical constituents, ignoring the relation of composition to histological structure.

This is most remarkable, since the methods of vegetable histology, as well as of chemistry, are invaluable in solving problems relating to the nature or constituents of foods, drugs, fibres and other products of vegetable origin. Sometimes one line of investigation alone is useful, sometimes the other, but often each throws some light on the subject, and the corroboratory results obtained by such widely differing means furnish an indisputable chain of evidence.

Let us look more closely into the nature and relation of these two applied analytical sciences.

Chemical analysis deals with chemical constituents ; microscopical analysis deals largely with the form of some of these constitu-

ents. Chemical analysis determines the amount of fibre, starch, protein, oil, etc.; microscopical analysis determines the shape, size, and other characteristics of the cells and cell contents. Chemical analysis usually stops with the mere determination of the amount of chemical constituents; microscopical analysis goes further and names the particular product from which they were derived. Chemical analysis answers a question only in scientific terms; microscopical analysis, in terms which all can understand.

In many cases, the best idea of a material is gained by following out both lines of investigation. By chemical analysis we learn the percentage of protein, fiber, starch, etc., but not the ingredients from which they were derived; by microscopical analysis we learn the ingredients, but usually gain only an approximate idea of their proportion. Given the results of both analyses, we may often calculate with some exactness the percentage of the different materials present.

If, for example, we find in a sample of wheat bran 11 instead of 16 per cent. of protein, and 15 instead of 8 per cent. of fiber, we know it is not pure bran but we do not know the adulterant; if we find corn-cob tissues under the microscope, we learn the adulterant but not the amount. Knowing that the material is a mixture of bran and ground corn-cob, and knowing the average percentage of protein and fiber in both, we are in a position to calculate from the results of the chemical analysis the relative amounts of these ingredients.

Again, if we find in ground mace 40 per cent. instead of 20 per cent. of fixed oil, we know it is not pure mace; if we find under the microscope a large amount of tissues of the Bombay mace, a material worthless as a spice containing about 60 per cent. of fixed oil, we learn the adulterant. Knowing all this, and knowing the average percentage of oil in true mace and Bombay mace, we have the data for calculating roughly the percentage of each in the mixture.

Still again, if in a textile fabric we find a certain percentage of organic fiber insoluble in boiling alkali, we know that the fabric is not all wool. If under the microscope we identify this insoluble fiber as cotton, we have found the missing link in the chain of evidence.

In the analysis of complicated mixtures, we must often rely entirely on microscopical examination. For example, chemical

analysis of a mixture of wheat, buckwheat and corn flours gives us little information, and it is only after the characteristic starch granules and tissues of each have been found under the microscope that we gain a definite idea of the nature of the constituents.

Again, in the examination of paper, the microscope is our sole dependence in learning the nature and approximate percentages of the fibers employed, chemical analysis serving merely to determine the kind and amount of sizing, coating and other non-fibrous constituents.

Among some condimental cattle foods examined by the writer some time since was one, the chemical analysis of which disclosed but one proximate constituent, viz., common salt; the microscope, however, disclosed linseed meal, corn meal, wheat feed, mustard hulls, cocoa shells, malt sprouts, fenugreek and turmeric. In such a case, dependence must be placed entirely on the microscope, except for mineral ingredients.

Chemical analysis of another sample demonstrated the presence of ground bone, carbonate of lime, iron oxide and free sulphur; microscopical examination disclosed linseed meal, wheat feed and charcoal. This is a striking example of a material in which half the constituents (all mineral) can only be detected by chemical analysis; the other half (all vegetable) by the microscope.

Many other equally striking examples of the interdependence of these two applied analytical sciences might be cited.

The point now arises as to who is to carry on these two lines of investigation so different in details but so similar in purpose.

One plan is for a chemist to make the chemical analysis and a botanist the microscopical examination. This plan has the advantage that each can confine his attention to one specialty, but it had the disadvantage that the close partnership between the two, which is essential to the best results, outside of large institutions, is both difficult and expensive. Such a division of labor would usually be as impracticable as to divide the work of a chemical laboratory between a chemist and a physicist, the former conducting the precipitations and other chemical processes, the latter, polarizations, determinations of specific gravity, refractive index and the like.

The rational plan is for one man to master both lines of research. Such a man need not execute all the details, but he should be thoroughly acquainted with them and should interpret the results. We will call him an analyst, not a chemist or a botanist, and his

laboratory an analytical laboratory, not a chemical or botanical laboratory. His equipment should consist of the necessary apparatus for a wide variety of chemical work and a complete microscopical outfit, including micro-reagents and a set of standard specimens of economic seeds, roots, barks, fibers, woods, etc.

But in order to have workers in this field, we must have suitable courses of instruction in our schools of science. The subject has a recognized place in many continental universities, particularly in the schools of medicine, pharmacy and hygiene, but outside of a few institutions, receives little attention in America.

The student who seeks to prepare himself for this field should take both chemical and botanical studies. In chemistry, he should study the branches taught in a well-regulated chemical course—elementary chemistry, qualitative and quantitative analysis, organic and physical chemistry, and so on. In botany he should take up successively elementary botany, systematic botany (at least of the phanerogams) and vegetable anatomy and physiology. These studies are all on the curriculum of every college and school of technology, although the student of chemistry does not usually take all the botanical studies named. Without a certain amount of botanical training, however, a chemist is no more fitted to take up microscopical analysis than a botanist without chemical training is fitted to work at quantitative analysis.

After his preliminary studies in chemistry and botany, the student is ready to take up a course in the methods for the chemical and microscopical examination of the various raw materials and of the products derived from them. This course should be so arranged that the student will carry along his chemical and histological practice side by side, as he must do afterwards in practical work. For example, in studying the cereal grains, he should devote part of his time to the methods of determining water, ash (including ash analysis), protein, fiber, starch, fat, pantosans, etc., and another part to a systematic study of the starches and the histological elements of the bran coats both in sections and in powdered form. In like manner, he should take up a chemical and histological study of leguminous seeds, oil seeds, spices, tea, coffee, cocoa, drugs, fibers, etc.

His work in the chemical laboratory should teach him not only the strictly chemical methods but also the use of the polariscope, the spectroscope and other physical apparatus, and his microscopical

instruction should fit him not only to differentiate organized forms but other characteristic elements, such as fat crystals, mineral crystals, and the like.

After such a course, he should be able not only to undertake investigations in physiological or plant chemistry but also the laboratory work of an official food department or a custom house, a flour mill, a brewery, a sugar refinery, a candy works, a fruit cannery, a drug mill, a textile mill, a paper mill, etc.

It is my firm belief that courses similar to that outlined should be conducted in all our leading universities and schools of technology, and the student should be taught the use of the microscope in conjunction with the balance in solving the analytical problems which every day become more numerous and intricate.

CORRESPONDENCE.

AN HISTORICAL MEDICAL EXHIBITION IN LONDON.

For the first time in 21 years the International Medical Congress will meet in London in the summer of 1913, and, in this connection, an exhibition of rare and curious objects relating to Medicine, Chemistry, Pharmacy and the allied sciences is being organized by Mr. Henry S. Wellcome. The response to the appeal for loans has been most successful, with the result that probably one of the most interesting collections of historical medical objects ever gathered together will be on exhibition during the meeting of the Congress.

Among other interesting sections is one including the medical deities of savage, barbaric and other primitive peoples. Through the kindness of friends, specimens of these have been forwarded from all parts of the globe, but there are still many gaps to be filled, and those who possess such objects, and would be willing to loan them, should communicate with the Secretary of the Exhibition, whose address is given below.

Amulets, talismans and charms connected with the art of healing will also form another prominent feature and any loans of this description would be welcomed.

In the section of surgery, an endeavor will be made to trace the evolution and development of the chief instruments in use at the present day, and it is desired to accumulate specimens of instru-

ments used in every part of the world by both savage and civilized peoples.

In pharmacy and in botany special exhibits are projected, which will include models of ancient pharmacies, laboratories and curious relics of the practice of alchemy in early times. Specimens of ancient and unusual materia medica from all parts of the world will also be exhibited.

A complete, illustrated syllabus will be forwarded to anyone interested on application to the Secretary, 54a, Wigmore Street, London, W. England.

DEAR SIR:

The Council on Pharmacy and Chemistry has appointed a Committee on Therapeutic Research, to encourage and assist the investigation of problems which promise to have some direct practical bearing on Therapeutics; especially such problems as require collaboration. The enclosed reprint will give you some idea of the objects of this committee.

The Committee would be pleased to receive suggestions from you; and if you should be doing or planning any work along this general line, the Committee would be glad to extend any assistance in its power. It would also invite your attention to the enclosed suggestive list of problems which appear to merit investigation. Perhaps you may find there some topic which would interest you or your colleagues. It is planned to entrust the responsibility for each investigation to experienced men who will be free to plan and conduct the research, select their collaborators, and publish the results. A limited fund has been appropriated by the Association for materials and technical assistance. The results may be reprinted in the "Reports" of the Council, or in special monographs devoted to each subject.

Respectfully yours,

TORALD SOLLMANN, *Chairman,*
DAVID L. EDSALL,
R. A. HATCHER,
W. A. PUCKNER, *Secretary,* 535 Dearborn Ave, Chicago, Ill.

The Committee has published a list of problems suggested for therapeutic investigation. Some of the subjects which are under investigation are the following:

Antiseptics and Germicides: Standardization.
Antiseptics, Intestinal: Efficiency of.

Cardiovascular Drugs: Detailed study of clinical actions by modern methods.

Chloroform: Effects of Impurities.

Digitalis Group: Cumulative action and absorption.

Iodides, relative efficiency and side effects of organic and inorganic.

Phosphorus Compounds: Critical literature.

Salicylates: Causes of idiosyncrasy.

Salicylates: Comparison of natural and synthetic.

[EDITOR.]

BOOK REVIEWS.

JAHRESBERICHT DER PHARMAZIE, herausgegeben vom Deutschen Apotheker Verein. Bearbeitet von Dr. Heinr. Beckurts unter Mitwirkung von Dr. H. Frerichs und Dr. H. Emde. 46 Jahrgang, 1911, Göttingen, Vandenhoeck & Ruprecht, 1912.

It is by no means presumptuous to assume that pharmacists who are at all conversant with the German language or with German pharmaceutical literature are also more or less familiar with the Jahresbericht der Pharmazie. To pharmacists who know the book it will perhaps not be necessary to say that the Jahresbericht for 1911 is fully equal to its predecessors. On the other hand, it would be futile to attempt to describe to pharmacists who are not familiar with the volumes of this widely known annual review of the literature of pharmacy, such a wonderfully comprehensive fund of information in the course of an ordinary book review. As a matter of record it will suffice therefore to state that the "Jahresbericht" for 1911 contains a total of 547 octavo pages, no less than 67 of which are devoted to a comprehensive double and in part triple column index, including approximately 8,000 references. In conformity with previous volumes the material is arranged under the general headings: I, Pharmacognosy; II, Pharmaceutical chemistry; III, Organotherapeutic and serum preparations; IV, Galenical preparations; V, Medical chemistry; VI, Chemistry of foods; VII, Toxicological chemistry. These several sections are followed by a reflection of the permanent literature, on pharmacy, of the year 1911, and the very complete and comprehensive index referred to above. An occasional typographical error, particularly in connection with the names of American authors, is somewhat annoying and may prove misleading to future generations of pharmaceutical workers who may have occasion

to look up the recorded work of any one individual. Aside from comparatively few shortcomings in this direction, however, the book is a really valuable contribution to the literature of pharmacy and as a book of references will be consulted for many years to come.

M. I. W.

DIGEST OF LAWS AND REGULATIONS IN FORCE IN THE UNITED STATES RELATING TO THE POSSESSION, USE, SALE AND MANUFACTURE OF POISONS AND HABIT-FORMING DRUGS. By Martin I. Wilbert and Murray Galt Motter. Prepared by direction of the Surgeon General. Washington, Government Printing Office, 1912.

This publication appears as Public Health Bulletin No. 56 and is evidently one of a series of Bulletins designed to present a comparative reflection of laws bearing on public health problems. Previous publications enumerated in the list of "Public Health Bulletins" include: Analysis of the laws and regulations relating to the organization powers and duties of health authorities: An analysis of the laws and regulations relating to vaccination: An analysis of the laws and regulations relating to ophthalmia neonatorum; and: A digest of the laws and regulations relating to the reporting of cases of sickness. The present publication is of immediate and direct interest to pharmacists and emphasizes, more than any one other available publication the pressing need for greater uniformity in Federal and State laws relating to the manufacture, sale and use of poisons and habit-forming drugs as well as a correlation of the food and drug laws designed to restrict the sale of articles that may contain or be contaminated with substances that can properly be considered as being poisonous or deleterious in any form.

Some idea regarding the comprehensiveness of the contained material may be had from the following list of tables that are included in the Introduction:

Table showing comparative number of cases of suicide and the number of deaths from acute and chronic poisoning and from alcoholism in the registration area, 1900 to 1910.

List of general definitions embodied in the laws designed to restrict the sale of poisons.

List of substances enumerated in the laws designed to restrict the sale of poisons.

Table showing the requirements embodied in the laws designed to restrict the sale of poisons.

Table showing requirements relating to the practice of pharmacy,

embodied in the several laws regulating the sale of poisons and narcotics.

Table showing the requirements embodied in the laws designed to restrict the sale and use of cocaine and narcotics.

Table showing the requirements relating to poisons and narcotics embodied in the several food and drug laws.

Table showing the requirements embodied in laws designed to restrict occupational intoxications.

The tables are followed by abstracts and references to Federal, State and Municipal laws and regulations relating to the subject matter of the Bulletin. The abstracts, in turn, are arranged uniformly under the headings: Sale and use of poisons: Sale and use of cocaine and narcotics: Drugs to be announced on label: Poisons in articles of commerce: Occupational intoxications: Methyl alcohol: Sale and use of intoxicating liquors: Practice of Pharmacy: and: Standards for drugs. All of the contained material is reviewed in a comparative way in an analytical index of 18 double column pages. As pointed out in the introductory paragraphs of this Bulletin the health and life destroying influences of poisonous substances are a more potent factor in undermining the public health than is generally appreciated or even suspected, despite the more than 8,000 deaths annually reported as being directly due to the ingestion or inhalation of poisonous substances. The material presented in the 278 pages of the pamphlet under discussion should be the cause for a public awakening to the possible dangers from the promiscuous sale and use of poisonous substances and the Bulletin should serve to direct the attention of druggists generally to the shortcomings evidenced in the several State laws, and lead them to insist that the safeguards for the protection of the health and lives of the public should be improved and strengthened and having done this they should insist that the laws be strictly enforced so that every death due to the ingestion or use of a poisonous substance be thoroughly investigated and the blame fixed on the person or persons whose laxity in selling or handling the poisonous compounds is at fault.

Copies of this Bulletin, to the limit of the edition, for free distribution, may be obtained by addressing the "Surgeon General, U. S. Public Health Service, Washington, D. C." Additional copies of the publication may be procured from the "Superintendent of Documents, Government Printing Office, Washington, D. C.," at 25 cents per copy.

EWEN McINTYRE.[1]

HONORARY PRESIDENT, COLLEGE OF PHARMACY OF THE CITY OF NEW YORK.[2]

In the death of Mr. Ewen McIntyre, which occurred on Wednesday, January 8, at his residence, 303 West 74 Street, the College of Pharmacy suffers one of the most severe and painful losses in its history. Mr. McIntyre was the oldest living graduate of this School, being a member of the class of 1847. He became a trustee of the College in 1873, vice-president in 1874 and president in 1876, in which office he continued until 1889. He then again entered the board of trustees, in which position he continued until 1892. In 1904 he was elected honorary president and continued to fill this office until the occurrence of his death.

Mr. McIntyre was one of the oldest living pharmacists of this city, if not actually the oldest. When he established his pharmacy at 18th Street and Broadway, his friends considered him reckless in moving so far out of the city, where residents were few and scattered. At that time little could be seen from his front door except pasture fields, enclosed by rail fences. During that period of small beginnings, he achieved business success by his habits of economy and industry, and prepared himself to take full advantage of the larger opportunities which came with the upward growth of the city. He withstood successfully all financial storms and scored a continuous success, retaining to the last his ownership of the valuable commercial site where he originally located, an act that well illustrates the habit of persistency and permanency that characterized his entire life.

His high and influential position in pharmacy, national as well as local, did not cease with his retirement from active business, but continued without intermission until his death, which met him as honorary president of the American Pharmaceutical Association.

His commercial honesty and honor were of the sterling and severe type of a former generation. His entire professional record fails to disclose any act which could be justly characterized as dishonorable or unprofessional. He was recognized far beyond the

[1] Reprinted from *Columbia University Quarterly*, March, 1913.

[2] A somewhat detailed biographical sketch of Mr. McIntyre appears in the *Druggist's Circular* for February, 1913.—Editor.

limits of the pharmaceutical world as a business man of sound credit and one whose word could be trusted to the uttermost, and in this way he will be remembered by thousands who survive him. To the physicians of this city, Mr. McIntyre has always been known as a pharmacist who respected the proper relations between the two professions and who represented the highest ideals and excellence in pharmaceutical practice.

It was Mr. McIntyre's discoveries of adulterated drugs in the New York market, and his energy in directing general attention to them, which led to the first federal legislation on this subject, to the official inspection of drug importations and, incidentally, to the formation of the American Pharmaceutical Association. Mr. McIntyre's interest in pharmaceutical education was early enlisted and grew steadily with his individual development. He watched its progress as a national institution, while he worked unremittingly for its local advancement. Perhaps the New York College of Pharmacy is his greatest monument, although that claim may well be contested by the American Pharmaceutical Association. He gave freely of both his time and money to protect and advance it at many stages of its career, and the conservation of its educational ideals is largely attributable to his steady support during various critical periods.

One of the most striking characteristics of this really great man was his ability to so easily take to himself each newly appearing generation, while retaining all of value that he had gained through his acquaintance with those who had preceded. His mind refused to bow to the psychological law of failure of the aged to perceive the new while clinging tenaciously to the memory of the past. He thus secured a place in the minds and hearts of the latest graduates in pharmacy that was hardly less secure than that which he retained with the aged. With all these persons he will continue to live in his death, and the influence of his character upon their lives must continue to be great.

Mr. McIntyre's religious life was one of steadiness and consistency. He lived his belief. Were there more to live as he did, there would be fewer to doubt the sufficiency of Christianity as the dominant power.

Personally, Mr. McIntyre was of the most sweet and cheerful disposition. Present trouble was with him always submerged in a confident and realizing faith in the future. His very entrance into

the presence of discouragement or sadness tended to dissipate it. The sight of his smiling face and the grasp of his hand were a never-failing stimulus, and their memory is an abiding reality.

H. H. RUSBY.

A TRIP TO EUROPE.[1]

During the last decade trips to Europe arranged by societies of all kinds have been undertaken with great success. Singing societies, veterans of the German army, teachers' associations, and various scientific societies have visited England, France, Germany and other parts of Europe and derived much pleasure and instruction from these trips.

These visits have been reciprocated by Europe, and a number of social and scientific societies from England and Germany have come to see our customs and institutions. No wonder, therefore, that American pharmacists should also think of such a journey, and the committee appointed by Dr. Ch. F. Klippert, the president of the German Apotheker-Verein of New York, and headed by Dr. W. C. Alpers is perfectly timely. Nor can there be any doubt that such an enterprise can best be undertaken by the Apotheker-Verein, whose members all speak two or more languages, and many of whom have visited Europe repeatedly and are therefore familiar with the travelling conditions of the various countries.

The idea of such a trip by pharmacists is not new. Some years ago, at the occasion of the world's fair at Paris, the American Pharmaceutical Association appointed a committee to submit plans, to visit the fair in a body and hold the meetings on the steamer during the trip across the ocean. But many members feared that in case of inclement weather these meetings might prove a failure and others did not like the idea that pleasure and entertainment should have a deciding influence on the selection of the place of meeting, and the project failed. A good financial plan was also lacking, and many feared the height of the expenses.

Profiting by the failure of that venture the present advocates of the plan hope to avoid these cliffs. In the first place, this is to be a general enterprise, open to every pharmacist and his friends, so that no constitution or by-laws of any existing society will be interfered with. As to the expense, it is true that but few of our

[1] Translated from an editorial in the "Apotheker-Zeitung."

fellow-pharmacists would be able to draw the full amount—at least $150 or $200 for each person—out of their business at one time, but with the aid of proper financiering this sum can be saved gradually. Suppose the trip will take place in two years, arrangements of regular monthly contributions can be made, which the contributor may withdraw at any time, if he will not join in the enterprise. Monthly payments of $5.00 would accumulate to more than half the required sum, and $10.00 monthly be more than sufficient to defray all expenses. Everybody knows that it is much easier to save $10.00 a month than to draw $200 at one time.

The trip itself would serve a double purpose; first, pleasure and recreation, and second, instruction and information, and each participant can follow his own inclination in this respect. The most beautiful parts of England, France and Germany—wherever the trip is planned—will be selected, and each one given full occasion to behold and admire whatever is worth seeing. Side-trips to points of interest to this one or that one will also be arranged. It may be supposed that the chemists, pharmaciens and Apotheker of the respective countries will contribute their share to the enterprise of the guests, so that the object of recreation will fully be reached.

At the same time, in planning the trip, due regard will be paid to information and instruction. Cities with world renowned chemical factories, like Elberfeld, Darmstadt, Hoechst, Leipzig, and others will be visited, in order to give the travellers an insight into the magnitude of the European chemical industry. Also universities and schools of technology that possess chairs of learning or laboratories of particular interest to pharmacists will not be omitted and these visits will be of particular interest to our teachers and professors.

At the return each traveller will have the privilege of staying longer with friends and relatives in Europe or to extend the trip to other countries. We believe that among the 45,000 pharmacists of the United States a sufficient number can be found, whose "Wanderlust" will make them join such an enterprise and we wish the appointed committee the best success.

NEW SOURCES OF TURPENTINE

Turpentine from western yellow pine, says the Department of Agriculture, can be put to the same uses as that from the longleaf pine of the southeast, which furnishes the bulk of the turpentine of commerce. Western yellow pine forms enormous forests in the

Rocky Mountain and Pacific Coast States, while the supply of longleaf is fast melting away. A product very similar to turpentine can be obtained also from pinon pine, another tree common in the southwest.

Careful tests made by the Department have shown that the yield of turpentine and rosin per season from western yellow pine in Arizona is only two-thirds that from the southeastern pine, the difference being due to the fact that the season of flow in the west is about 25 weeks, and in the south about 33 weeks. During the Civil War, when turpentining operations in the south had virtually ceased, some operations were carried on in California to meet local needs. But with the return of the southern product to the California market, the western operations were abandoned.

The results of a chemical examination of the oils of western yellow, pinon, digger, sugar, and lodgepole pines which have just been published by the Forest Service in an official bulletin show the possibilities of the rosin and turpentine from western yellow and pinon pines as a supplement to the present supplies. Economic problems of markets, transportation, and labor remain to be solved. Information as to how the Forest Service secured the yields upon which the analyses were based is given in another bulletin on the possibilities of western pines as a source of naval stores.

UTILIZATION OF ATMOSPHERIC NITROGEN.

A bulletin, giving the results of investigations of chemical industries made by Consul Thomas H. Norton, of Chemnitz, Germany, detailed as commercial agent of the Department of Commerce and Labor, has been issued recently by the Bureau of Foreign and Domestic Commerce. It is entitled, "Utilization of Atmospheric Nitrogen," and deals with the efforts that are being made to release the manufacturing and agricultural interests of the world from dependence upon natural sources of nitrates, particularly the saltpeter deposits of Chile. The most decided progress is being made by chemists in Germany, Scandinavia, France, Switzerland, and Austria, and the bulletin furnishes as accurate and comprehensive data as possible of the results thus far obtained by European chemists in their efforts to increase the supply of nitrogen.

Copies of this bulletin (Special Agents Series No. 52) may be obtained upon application to the Bureau of Foreign and Domestic Commerce, at Washington.